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CASE REPORT

Hiroshi Ouchi · Masaki Fujita · Satoshi Ikegame
Ichiro Inoshima · Eiji Harada · Yoichi Nakanishi

Successful treatment of refractory chronic necrotizing pulmonary aspergillosis with micafungin

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Abstract A 63-year-old man was admitted to our hospital because he complained of fever and productive cough; this was associated with cavitary infiltrates on his chest X-ray. Although several antibiotics were given, his symptoms did not improve. Bronchofiberscope investigation yielded *Aspergillus fumigatus*; thus, he was diagnosed with chronic necrotizing pulmonary aspergillosis. Itraconazole, 200 mg/day, was given, and his symptoms and infiltrates on chest X-ray gradually improved. After 2 months of treatment, new infiltrates appeared on a chest X-ray. Antibacterial agents had also shown no effect, and voriconazole was substituted for itraconazole. However, the infiltrates progressed in spite of the voriconazole administration. We added micafungin to the voriconazole treatment. Both his symptoms and the infiltrates on chest X-rays improved. Because voriconazole is thought to be the most effective agent against *Aspergillus spp.*, it is difficult to treat cases that are refractory to voriconazole. The treatment of this case provides invaluable information on how to treat pulmonary aspergillosis related to diseases other than hematologic malignancies.

Key words Lung aspergillosis · Voriconazole · Micafungin

Introduction

Pulmonary aspergillosis is an infectious disease caused mainly by *Aspergillus fumigatus*, and sometimes by *A. niger, A. flavus*, and *A. glaucis*. This pathogen causes three forms of pulmonary disease: saprophytic, allergic, and invasive.[1] Pulmonary aspergillosis is difficult to treat and is rapidly fatal, especially in the form of invasive disease. Chronic necrotizing aspergillosis, known as semiinvasive, is usually a slowly progressive form of invasive aspergillosis, although it sometimes spreads rapidly. Recently, new antifungal agents against aspergillosis have been introduced. We experienced a case of chronic necrotizing aspergillosis that was refractory to voriconazole and was, fortunately, successfully controlled by the addition of micafungin.

H. Ouchi · M. Fujita (✉) · S. Ikegame · I. Inoshima · E. Harada · Y. Nakanishi
Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashiku, Fukuoka 812-8582, Japan
Tel. +81-92-642-5378; Fax +81-92-642-5389
e-mail: fujita@kokyu.med.kyushu-u.ac.jp

Case report

A 63-year-old man complained of fever, general fatigue, and productive cough on December 19, 2005. He had had right upper lobectomy of the lung due to bronchiectasis at age 50 years, gastrectomy due to gastric cancer at age 59, and pneumonia at age 59. On admission, he was diagnosed with pneumonia and antibiotics were started; however, no improvement was achieved. Bronchofiberscopy specimens revealed *A. fumigatus*; thus, the disease was confirmed to be pulmonary aspergillosis, of the chronic necrotizing type. Itraconzole (200 mg/day) was started on January 6, 2006, and his symptoms and clinical signs improved. He was discharged and itraconazole was continued.

On March 3, 2006, new infiltrates appeared on a chest X-ray. Antibiotics were given in addition to itraconazole, but the infiltrates continued to progress gradually. He was admitted to hospital for more detailed investigation on March 24, 2006.

Physical examination revealed a coarse crackle in the right middle and lower lung fields. There was no marked sign of other organ involvement. Laboratory data on admission are shown in Table 1. Chest X-ray on admission (Fig. 1B) revealed progression of the cavity wall thickness and of the infiltrates around the cavity, with the appearance of new infiltrates, compared with the findings on the chest X-ray taken at the outpatient clinic (Fig. 1A). Chest computed tomography (CT) demonstrated findings similar to those on the admission chest X-ray–cavitary changes and infiltrates

Table 1. Laboratory data on admission

Hematology		Coagulation	
		PT	16.4/12.4 s
WBC	8380/μl	PT-INR	1.38 INR
Neut	86.8%	APTT	41.7/36.0 s
Lym	10.1%		
Mono	2.0%	Arterial blood gases (room air)	
Eos	1.0%	pH	7.443
Baso	0.1%	PaO_2	90.2 Torr
RBC	3.07×10^6/μl	$PaCO_2$	39.3 Torr
Hb	8.6 g/dl	BE	2.7 mmol/l
Pl	26.3×10^4/μl	SaO_2	95.2%
Serum chemistry			
TP	7.6 g/dl	Sputum examination	
Alb	3.2 g/dl	Bacteria	
T-Bil	0.4 mg/dl	*Aspergillus fumigatus*	
GOT	23 IU/l	*Candida albicans*	
GPT	20 IU/l	Ant-fast bacilli	Negative
LDH (L)	175 U/l	Tbc-PCR, negative	
ALP	31 IU/l	MAC-PCR, Negative	
BUN	19 mg/dl		
Cr	0.77 mg/dl		
Na	134 mEq/l		
K	3.5 mEq/l		
Cl	96 mEq/l		
Glu	92 mg/dl		
HbA1c	6.7%		
Immunology			
CRP	10.59 mg/dl		
β-D glucan	25.42 mg/dl		
Aspergillus Ag	0.2		

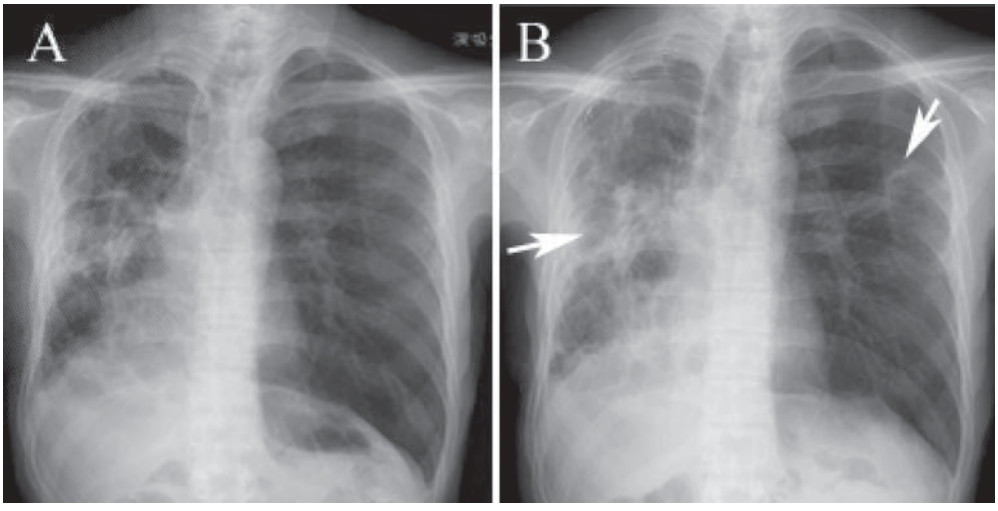

Fig. 1A, B. Chest X-rays. **A** Chest X-ray taken at outpatient clinic; infiltrates were seen mainly in the right lower lung fields. **B** Chest X-ray on admission; infiltrates have progressed in the right lower lung field as well as the left lung field (*arrows)*

in the left S3, S8, and S10, as well as bilateral pleural effusion.

Because we considered that the patient's chronic necrotizing aspergillosis was worsening, voriconazole was substituted for itraconazole. Bacterial pneumonia was not ruled out, so that tazobactam/piperacillin followed by biapenem was added. However, the infiltrates progressed, as shown in Fig. 2A. Chest CT revealed fluid accumulation in addition to the developing infiltrate. Notably, new cavitary changes appeared in the left lung fields (Fig. 2B). His symptoms also worsened, with the development of dyspnea and anorexia. Because the administration of voriconazole alone as an antifungal agent was considered to be ineffective, we added micafungin 150 mg/day to the voriconazole. Four days after the commencement of the micafungin administration, his fever was reduced. Laboratory data on inflammation were also improved. As shown in Fig. 3, chest CT documented the marked absorption of infiltrates; decrease of cavity size and decrease of the pleural effusion were also seen. Micafungin and voriconazole were continued for 1 month. He